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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Hoi-Ying N. Holman
Serial No.	:	10/582,422 – Conf. #4848
Filed	:	June 9, 2006
For	:	CATHETER-BASED MID-INFRARED REFLECTANCE AND REFLECTANCE GENERATED ABSORPTION SPECTROSCOPY
Art Unit	:	3768
Examiner	:	Brutus, Joel F

March 31, 2010

Commissioner for Patents
P.O. Box 1450
Alexandria, VA. 22313-1450

RULE 132 DECLARATION

Sir:

1. I am the named inventor of the presently claimed subject matter for the above-identified patent application.

2. I have read and are thoroughly familiar with the specification and pending claims, and I have reviewed the Office Action of December 1, 2009.

3. It is my understanding that the Examiner has rejected pending claims 29-40 and 42-50 under 35 U.S.C. §103(a) over U.S. Patent No. 5,293,872 (hereinafter Alfano) alone or in view of U.S. Publication No. US 2002/0164810 (hereinafter Dukor). The Examiner has also

rejected pending claim 41 under 35 U.S.C. §103(a) over Alfano in view of Dukor as applied to claim 34, further in view of U.S. Patent No. 4,817,013 (hereinafter Corenman).

4. It is also my understanding that the claims referred to by the Examiner in the Office Action of December 1, 2009 have been amended and a new set of claims have been submitted to the Patent Office.

5. The presently claimed invention relates to methods and apparatus for *in vivo* detecting and characterizing conditions in abnormal tissues that present in vascular diseases, in particular, atherosclerosis, by using reflection-based mid-infrared (IR) spectroscopy. Through the use of a catheter having a light source that emits light in the mid-IR region, reflectance spectrographs and reflectance generated absorption spectrographs of segments of normal tissues and tissues with atherosclerosis were collected and compared. The pathophysiologic features of disease states in tissue can be observed by increases in reflectance and in the numbers of reflectance generated absorbance peaks in the range of wavenumbers 4000 to 400 cm^{-1}. More specifically, increased absorbance peaks are within at least one range of mid-infrared wavenumbers selected from the group of: about 3500-3000, about 3020-3000, about 2950-2800, about 1800-1450, about 1710-1760, about 1690-1610, about 1520-1500, about 1480-1450, about 1100-900 and about 900-400 cm^{-1}. These mid-IR spectral bands can be used as diagnostic marker for atherosclerotic disease to develop a catheter-based diagnostic method and apparatus to detect and characterize sites of atherosclerosis. Moreover, the presently claimed invention is particularly adapted for use in the diagnosis of atherosclerotic plaques because it relies on two key elements discovered by us (Holman et al., 2008). Firstly, mid-infrared light that enters normal tissues is strongly absorbed by interstitial water and thus little infrared signals are detected (Figure 1a). Secondly, mid-infrared light that enters atherosclerotic tissues is reflected

because of the unque intrinsic optical properties of atherosclerotic constituents (lipids, cholesterol, calcified deposits) inside atherosclerotic tissues which convert the atherosclerotic tissue into a highly reflective matrix (Figure 1b). We believe that the fundamental of this invention is different from other methods previously known, as explained below.

6. With respect to the Examiner's 35 U.S.C. §103(a) rejection of pending claims 29-40 and 42-50 over Alfano alone or in combination of Dukor, none of the references cited by the Examiner teaches the use of signature mid-IR spectral bands as diagnostic marker for atherosclerotic disease. Since the amended claim 29 directs to a method of characterizing atherosclerosis conditions in tissues by examining the spectral features at the specific mid-IR spectral regions, I believe that the §103(a) rejection does not apply to the newly submitted claims.

7. Furthermore, Alfano discloses a method for detecting atherosclerotic tissues by measuring Raman scattered light. Unlike the present invention, this Raman spectroscopy method is based on spontaneous inelastic scattering (also called spontaneous Raman scattering) of monochromatic laser light emitted in the visible, near-infrared, or near ultraviolet range. The monochromatic laser light interacts with the electron cloud and the bonds of a molecule, and the interaction is such that the molecule is excited from the ground state to a virtual energy state. When the molecule relaxes and returns to a different vibrational state, it emits a photon. The difference in energy between the ground state and the new state leads to a shift in the emitted photon's energy (in frequency) away from the excitation energy (also in frequency). Light that re-emitted is collected with a lens and sent through a monochromator which only allows inelastically scattered light to enter the detector. The intensity of inelastically scattered light by the tissues is very low (about one per 10^7 incoming photons), and tissues also suffers

interferences from background autofluorescence signals because tissues tend to fluoresce when illuminated with visble light. In contrast, the reflection-based mid-IR spectroscopy used by the present invention involves reflected infrared light with strong signal (about one per 10^2 incoming photons), relies on the energy exchange between incident mid-infrared light with vibrational motion of atoms in the molecules, and does not share the background tissue autofluorescence problem. Finally, Raman effect depends strongly on the electron cloud and the bonds of the molecule, it is less sensitive to molecules with polar bonds and functional groups, which is important in diagnosis for atherosclerotic tissues.

8. In addition, the reflectance technique employed by the present invention is particularly suited for atherosclerosis imaging, not for other diseases, such as carcinomas. This is based on our discovery that the physical and chemical changes in the tissue environment, specific to the atheromatous plaques, make the plaques become an IR light reflector . As illustrated in our publication (Holman et al., 2008), water-rich native tissues have an average refractive index of approximately 1.35 – 1.38 (by extrapolation from literature) (Dirckx et al., 2005), whereas the average refractive index of lipid materials can vary from 1.45 to 1.50, depending on the composition and sizes of lipid particles (Maltsev et al., 1997). Additionally, the calcium deposits like hydroxylapatite or calciumphosphate which are common in atherosclerotic lesions (Stary, 2001; Schwarz et al., 2000), also have a significantly higher average refractive index of 1.63 and higher (Tarasevich et al., 2003). Experimental data have demonstrated that incident light that penetrates the diseased intima, composed of various amounts of lipid-rich materials and calcium deposits, can encounter multiple refractive boundaries because of multiple interfaces (Figure 2). In addition, our experimental data demonstrated the existence of significant mid-IR reflectivity at sites of atherosclerosis in

harvested aortas from ApoE knockout mice. (Figure 1b versus Figure 1a) In contrast, tissues present in carcinoma don't contain lipid-rich materials, calcium deposits, or other components that are common in atherosclerotic lesions. Incident infrared light is strongly absorbed by tissue water (>70% of tissue content is water), and thus behave like an IR light absorber instead of a reflector. Therefore, the reflectance technique of the present invention cannot be used to detect and characterize carcinoma tissues. Dukor discloses a method and system for diagnosing carcinoma by using IR spectroscopy, not reflective IR spectroscopy. Dukor does not teach or suggest using the reflective IR spectroscopy technique to diagnose atherosclerosis. In addition, the reflective IR spectroscopy as in the present invention can't be applied to carcinoma diagnosis at all. Therefore, there was no reason for a person of ordinary skill in the art to combine Dukor with Alfano for atherosclerosis detection.

9. Regarding the Examiner's §103 (a) rejection of pending claim 41 over Alfano in view of Dukor as applied to claim 34, further in view of Corenman, none of the references cited by the Examiner teaches or shows the signature spectra in the specific narrow wavenumber regions identified in the present invention.

10. In addition, as discussed above, Dukor does not teach or suggest using the reflective IR spectroscopy technique to diagnose atherosclerosis. Moreover, the reflective IR spectroscopy of the present invention is especially adapted to atherosclerosis detection, and can't be applied to carcinoma identification, which is the subject of Dukor. Therefore, a person of ordinary skill in the art would not have been motivated to combine Alfano and Dukor in the first place. Neither does Corenman teach the use of reflection based mid-IR spectroscopy for atherosclerosis characterization. In our opinion, it would be unobvious for a skilled artisan to

combine those references and employ reflective IR spectroscopy method and apparatus to detect atherosclerosis.

11. To summarize, none of the references cited by the Examiner discloses, teaches, or suggests, individually or in combination, the method and apparatus for detecting, characterizing and imaging atherosclerosis tissues by using reflection-based mid-IR spectroscopy. Neither of these references discloses, teaches, or suggests, individually, or in combination, the use of signature mid-IR spectral bands as diagnostic marker for atherosclerotic disease. Not only that, the use of mid-IR reflectance and reflectance generated absorption spectroscopy according to the presently claimed invention is particularly suited for probing atherosclerotic conditions due to the presence of highly reflective constituents inside atherosclerotic tissues. The same technique can't be applied to diagnosis of carcinoma, or other diseases, due to a lack of the similar reflective features. In our opinion, a skilled artisan at the time of invention would not have motivation to use reflection-based mid-IR spectroscopy to characterize atherosclerosis tissues based on the references cited by the Examiner. Likewise, a person of ordinary skill in the art at the time of the invention would not have expected to use the signature mid-IR spectral bands, according to the present invention, as diagnostic marker for atherosclerotic disease. Therefore, none of the references cited by the Examiner, alone or in combination, renders the present invention obvious.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

By Hoi-Ying Holman
Name Hoi-Ying N. HOLMAN

03/31/2010
Date

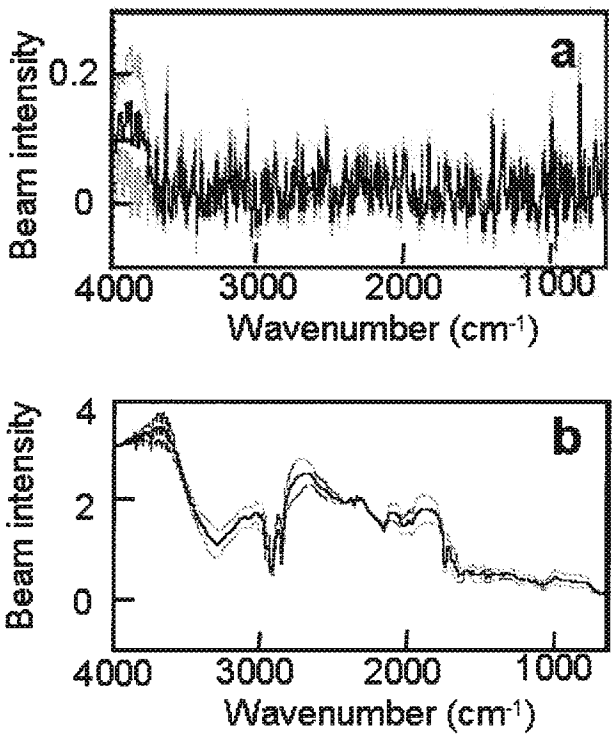

Figure 1. Infrared reflectivity from (**a**) non-atherosclerotic versus (**b**) atherosclerotic sites. Each plot shows the averaged spectrum (black trace) ± 1.0 standard deviation (gray trace); n = 26. (Holman et al., 2008)

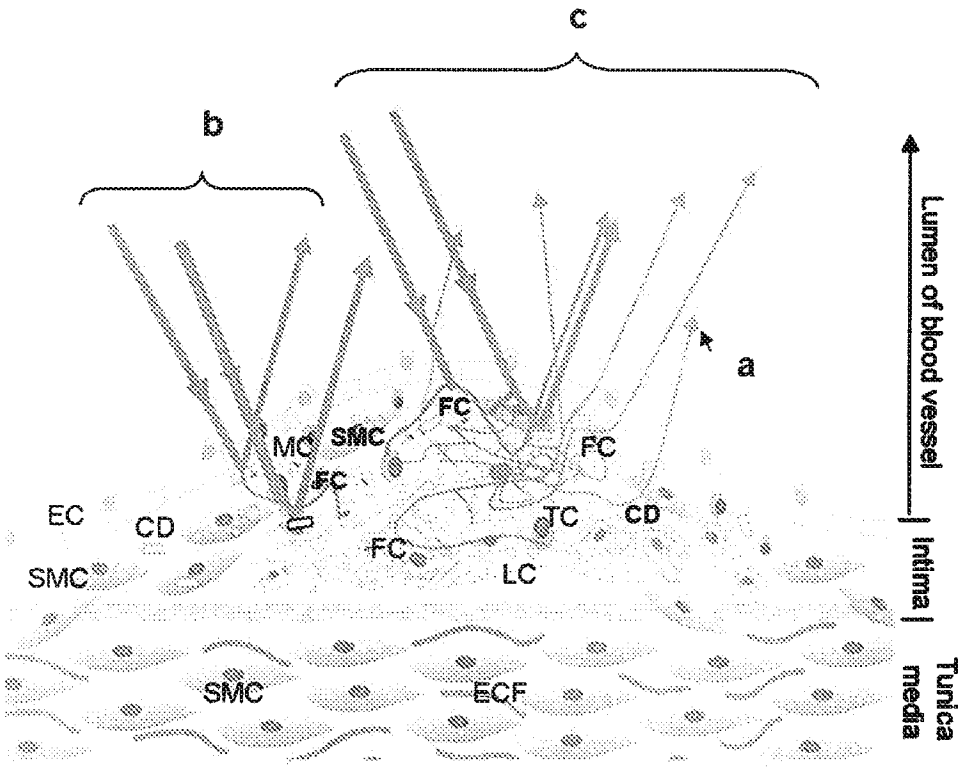

Figure 2. An atheromatous plaque as an infrared light reflector: a graphic description of the reflection mechanisms . A hypothetical diagram showing the ways in which the incident mid-IR light might behave when hitting the atherosclerotic lesion. (**a**) Diffuse reflection: if the surface roughness at the refractive boundary is much larger than the wavelength, the light can undergo both multiple diffuse reflections and absorptions before re-emerging where it can be detected. The reflectance is generally very small (< 1%, see text). (**b**) Quasi-specular reflection: If the surface roughness at the refractive boundary is smaller than the wavelength (i.e., the surface is nearly smooth, for example, like the surface of mineral deposits), the light can experience a quasi-specular reflection before remerging. Depending on the orientation of the surface of the mineral deposit, the reflectance can generally be quite significant. (**c**) Mixed diffuse and quasi-specular reflection: as demonstrated by our measurements, the surface roughness at the refractive boundary is such that a summed contribution from both the quasi-specular reflection and the diffuse reflection, although it is dominated by the much stronger quasi-specular reflection. CD, calcium deposits; EC, endothelial cells; ECF, extracellular collagen fiber; FC, foam cells; MC, macrophages; LC, lipid particles and lipid core; SMC, smooth muscle cells; TC, T-cells. Arrows and lines, Infrared light paths.